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Rearrangement of N-alkyl 1,2-amino alcohols. Synthesis of (S)-toliprolol and (S)-propanolol

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1. Introduction

The 1,2-amino alcohol functionality is present in a wide variety of natural products and biologically active compounds. Of particular importance, are the optically active N-isopropyl-3-(aryloxy)-2-hydroxypropylamines A. This family of more than 30 β-adrenergic antagonists is used in the therapy of hypertension, glaucoma, angina pectoris, anxiety, and obesity. These N-isopropyl-3-(aryloxy)-2-hydroxypropylamines, such as (S)-toliprolol I and (S)-propanolol II, are mainly active as the (S)-enantiomers. For example, the (S)-propanolol II is 100-fold more active than the (R)-stereoisomer 4 (Fig. 1).

Several syntheses of homochiral β-adrenergic blocking agents of type A have been achieved mainly through the formation of either the C1–N bond (pathway a) or the C3–O bond (pathway b). The third pathway (pathway c) corresponds to a reductive amination of A (Scheme 1). The key chiral epoxides can be readily obtained via enzymatic resolution, nitroaldol reaction, asymmetric ring opening of aryl glycidyl ethers, Sharpless asymmetric epoxidation or asymmetric dihydroxylation. An asymmetric synthesis has also been achieved utilizing the chiral pool.

Recently, we have shown that linear N,N-dialkyl 1,2-amino alcohols C were obtained by rearrangement of N,N-dialkyl β-amino alcohols B 7 by treatment with a catalytic amount of TFAA 8 or with

![Figure 1](image1.png)

![Scheme 1](image2.png)
a catalytic amount of sulfuric acid. The rearranged N,N-diarylalkylamino compounds C can be transformed to N-alkylamino alcohols D, but this strategy necessitates a deprotection step, which is not atom economical. In order to avoid these protection/deprotection steps, the direct rearrangement of N-alkyl 1,2-amino alcohols of type E has been considered (Scheme 2).

![Scheme 2. General scheme.](image)

Here, we would like to report our results concerning the rearrangement of N-alkyl 1,2-amino alcohols of type E and the application of this rearrangement to the synthesis of (S)-toliprolol I and (S)-propanolol II.

2. Rearrangement of N-alkyl 1,2-amino alcohols

At first, N-alkyl β-amino alcohols 1 and 2 were examined under the catalytic acidic conditions that were previously developed for the rearrangement of N,N-dialkyl β-amino alcohols. Thus, when 1 and 2 were treated with H2SO4 (0.05 equiv), respectively, for 2 h and 24 h, at 180 °C in THF under microwave irradiation, 3 (22%) and 4 (42%) were obtained in poor yields (Scheme 3).

![Scheme 3. Rearrangement of N-alkyl β-amino alcohols 1 and 2 with H2SO4.](image)

Due to these results, rearrangement of compound 2 was examined under different conditions in order to improve the yields in the rearranged product 4. Other reagents such as TFA and TFAA were used in catalytic amount to rearrange N-alkylamino alcohol 2 (THF, microwave irradiation, 24–30 h). However, the yields in the rearranged amino alcohol 4 were modest (54–57%) (Table 1, entries 1 and 2). The best yield in 4 (78%) was obtained by using a stoichiometric amount of TFAA and Et3N at 120 °C for 12 h under microwave irradiation, followed by the addition of NaOH (Table 1, entry 3).

![Table 1](image)

Furthermore, if one considers the mechanism of the rearrangement of E into β-amino alcohol D using a catalytic amount of TFAA, the first steps will be identical to the rearrangement using a stoichiometric amount but an additional step, a transamidification between compound I and amino alcohol E can occur to complete the catalytic cycle by generating the rearranged amino alcohol D and the trifluoroamide. This latter can be involved in the formation of ester F. The mechanism of the rearrangement to the synthesis of (S)-toliprolol I and (S)-propanolol II.

![Scheme 4. Supposed mechanism for the rearrangement of E with a stoichiometric amount of TFAA and Et3N.](image)

As the conditions of the rearrangement of N-alkyl β-amino alcohols are more drastic (higher temperature and longer reaction...
time) in utilizing a catalytic amount of TFAA than in utilizing a stoichiometric one, the use of 1 equiv of TFAA and 1 equiv of Et3N in THF for 12 h at 120 °C followed by the addition of NaOH was chosen as conditions to study the rearrangement. When these conditions were applied to β-amino alcohol 2 and commercially available compound 5, the corresponding rearranged compounds 4 and 6 were, respectively, obtained in good yields (> 78%) but, very disappointingly, the enantiomeric excesses were low, 30% for compound 4 and 46% for compound 6 (Scheme 6).

![Scheme 5. Supposed mechanism of the rearrangement of E with a catalytic amount of TFAA.](image)

In order to verify this hypothesis, the rearranged β-amino alcohol 6 possessing an enantiomeric excess of 99% was transformed to amidoester 7 [TFAA (2.2 equiv), Et3N (2.2 equiv), THF, rt]. This latter was then treated with 1 equiv of triethylammonium trifluoroacetate, in THF under microwave irradiation at 120 °C. After 12 h, the reaction media was treated with NaOH and 6 was isolated in 80% yield with an enantiomeric excess of 24%, demonstrating that the trifluoroacetate anion present in the reaction media can attack 7 according to an SN2 mechanism leading to the racemization of 6 (Scheme 8).

![Scheme 7. Supposed mechanism of racemization.](image)

Based on the proposed mechanism, we would not expect to see this sort of epimerization. An hypothesis can be proposed to explain this racemisation. After the rearrangement, several species can be present in the reaction media such as H, I, and J, this latter can be formed from H and I. The epimerization can occur in species J according to an Sn2 mechanism involving a trifluoroacetyl anion that can be delivered from triethylammonium trifluoroacetate, which is present in the reaction media (Scheme 7).

![Scheme 6. Rearrangement of β-amino alcohols 2 and 5. *Determined on the dibenzylated compound 19 and the benzylated compound 22 (cf. Scheme 10).](image)

Furthermore, in order to prove that in the absence of the triethylammonium trifluoroacetate in the reaction media the racemization does not occur, trifluoroamide 8 was synthesized from 5 [TFAA (1 equiv), Et3N (1 equiv), THF, rt] and then heated in THF under microwave irradiation at 120 °C for 12 h without triethylammonium trifluoroacetate. The reaction media was then treated with NaOH and 6 was isolated in 43% yield with an enantiomeric excess of 98%. These experiences demonstrated that triethylammonium trifluoroacetate was involved in the racemization process of 6. Unfortunately, the lack of this ammonium salt entailed a moderate conversion in 6 (54%), demonstrating that triethylammonium trifluoroacetate is probably involved in the mechanism.
and/or the kinetic of the rearrangement (Scheme 9). Rising the temperature of the reaction to improve the conversion in 6 unfortunately came with the racemization of this latter.

![Scheme 9. Synthesis and rearrangement of β-amido alcohol 8.](image)

In order to obtain the best yield and enantiomeric excess in 6, the temperature and the reaction time were examined. The best conditions were 1 equiv of TFAA and 1 equiv of Et3N at 100 °C under microwave irradiation for 15 h. It is worth noting that when heated at 110 °C under microwave irradiation for 6 h, 5 was transformed into 6 with a very good enantiomeric excess (94%) and with a good yield (72%). The results are reported in Table 2.

### Table 2

Optimization of the temperature and reaction time for the rearrangement of 5

<table>
<thead>
<tr>
<th>Entry</th>
<th>Time (h)</th>
<th>Temperature (°C)</th>
<th>% ee</th>
<th>Yield (ee%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6</td>
<td>120</td>
<td>100</td>
<td>89 (46)</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>120</td>
<td>95</td>
<td>78 (87)</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>180</td>
<td>100</td>
<td>72 (64)</td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>110</td>
<td>91</td>
<td>72 (94)</td>
</tr>
<tr>
<td>5</td>
<td>15</td>
<td>100</td>
<td>84</td>
<td>63 (96)</td>
</tr>
</tbody>
</table>

* Determined on the dibenzylated compound 19 (cf. Scheme 10).

It is worth noting that for each substrate, the conditions have to be tuned up. The best conditions and results in obtaining 3, 4, 14–18 from, respectively, 1, 2, 9–13 are reported in Table 3.

The enantiomeric excesses of compounds 3, 4, 14–18 were found to be superior to 93% when amino alcohols 1, 2, 9–13 were heated at 110 °C or 120 °C for 6 h to 12 h.

The enantiomeric excesses of compounds 3, 4, 6, 14–18 were determined by measuring the enantiomeric excesses of either the dibenzyl β-amino alcohols 19–21 or the benzylalkyl β-amino alcohols 22–24. Preparations of 19–24 are reported in Scheme 10.

### 3. Synthesis of (S)-toliprolol and (S)-propanolol

The rearrangement of N-alkyl β-amino alcohols was then applied to the synthesis of (S)-toliprolol and (S)-propanolol, two β-adrenergic blocking agents, which are active as the (S)-enantiomers. The synthesis of these N-isopropyl-3-(aryloxy)-2-hydroxypropylamines would be obtained by rearrangement of 1,2-amino alcohols K that would be synthesized from d-serine methyl ester via the protected amino alcohol 25

![Scheme 11. Retrosynthetic approach to (S)-toliprolol and (S)-propanolol.](image)

The common intermediate 25 was synthesized in three steps from d-serine methyl ester. After carboxylation [CbzCl (1.1 equiv), K2CO3 (3 equiv) in THF/H2O 1/1], protection of the hydroxy carbamate [APTS, 2,2-dimethoxypropane] and reduction [NaBH4, THF/MeOH], 25 was isolated in 59% yield. In order to synthesize (S)-toliprolol, 25 was treated with m-cresol under the Mitsunobu conditions (PPh3, DEAD, toluene, 80 °C, 18 h) and the obtained aryl ether 26 (69%) was hydrogenated (H2, Pd/C 10%, MeOH) producing amino alcohol 27 (77%). This latter was rearranged to (S)-toliprolol by treatment with TFAA (1 equiv), Et3N (1 equiv) in THF under microwave irradiation at 110 °C for 12 h followed by the addition of NaOH. Under these conditions, (S)-toliprolol was isolated in 69% yield and with an enantiomeric excess of 92% (Scheme 12).
Similarly, (S)-propanolol was synthesized from 25. After a Mitsunobu reaction with α-naphthol leading to the aryl ether 28 (67%), classical hydrogenation (H2, Pd/C 10%, MeOH) of this latter produced the amino alcohol 29 in poor yield (33%). When the hydrogenation was conducted in a flow manner using H-Cube™ (Thales Nanotechnology Inc.), the amino alcohol 29 was isolated in a better yield of 75%. This latter was rearranged by treatment with TFAA (1 equiv), Et3N (1 equiv) in THF under microwave irradiation at 110 °C for 12 h followed by the addition of NaOH leading to (S)-propanolol in 60% yield, with an enantiomeric excess of 92% (Scheme 12).

4. Conclusion

The rearrangement of optically active N-alkyl 1,2-amino alcohols can take place by treatment of these latter with TFAA, Et3N (1 equiv). For each substrate, the temperature and the reaction time have to be controlled in order to obtain the best yield and enantiomeric excess in the rearranged products. This simple rearrangement can be applied to the synthesis of biologically active compounds in an efficient manner.

### Table 3
Rearrangement of N-alkyl β-amino alcohols

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting material</th>
<th>Time (h)</th>
<th>Temperature (°C)</th>
<th>Product</th>
<th>Yield (ee) [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>OH NHBn (S) PH</td>
<td>12</td>
<td>120</td>
<td>14 OH NHBn (R)</td>
<td>70 (98)a</td>
</tr>
<tr>
<td>2</td>
<td>OH NH (S) PH</td>
<td>12</td>
<td>120</td>
<td>15 OH (R)</td>
<td>80 (96)a</td>
</tr>
<tr>
<td>3</td>
<td>NH (S) OH</td>
<td>6</td>
<td>110</td>
<td>4 (R) Ph</td>
<td>85 (94)b</td>
</tr>
<tr>
<td>4</td>
<td>OH NH (S) Ph</td>
<td>6</td>
<td>110</td>
<td>16 (R) Ph</td>
<td>91 (96)</td>
</tr>
<tr>
<td>5</td>
<td>NH (S) OH</td>
<td>12</td>
<td>120</td>
<td>17 (R)</td>
<td>78 (93)</td>
</tr>
<tr>
<td>6</td>
<td>OH NHBn (S) OH</td>
<td>12</td>
<td>18</td>
<td>3 (R) NHBn</td>
<td>88 (93)a</td>
</tr>
<tr>
<td>7</td>
<td>OH (S) OH</td>
<td>8</td>
<td>120</td>
<td>18 (R)</td>
<td>74 (93)</td>
</tr>
</tbody>
</table>

a Determined on the dibenzylated compounds 20, 21 (cf. Scheme 10).
b Determined on the benzylalkyl β-amino alcohols 22–24 (cf. Scheme 10).
5. Experimental

5.1. General

TLC was performed on Merck 60F254 silica gel plates and visualized with a UV lamp (254 nm), or by using a solution of KMnO₄/K₂CO₃/NaOH in water followed by heating. Column chromatography was performed with Merck Geduran Si 60 silica gel (40–63 μm). Infrared (IR) spectra were recorded on a Bruker Tensor™ 27 (IRFT), wave numbers are indicated in cm⁻¹. ¹H NMR spectra were recorded on a Bruker AVANCE 400 at 400 MHz and data are reported as follows: chemical shift in parts per million from tetramethylsilane as internal standard, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, h=heptuplet, m=multiplet or overlap of non-equivalent resonances, integration). ¹³C NMR spectra were recorded on a Bruker AVANCE 400 at 100 MHz and data are reported as follows: chemical shift in parts per million from tetramethylsilane with the solvent as internal standard (CDCl₃, δ 77.0 ppm), multiplicity with respect to proton (deduced from DEPT experiments, s=quaternary, C, d=CH₂, t=CH₃, q=CH₂), Mass spectra with electronic impact (MS-EI) were recorded from a Hewlett-Packard tandem 5890A GC (12 m capillary column)–5971 MS (70 eV). All reactions were carried out under argon atmosphere. Commercially available reagents and solvents were used as received. Anhydrous solvents were distilled: tetrahydrofuran and diethyl ether were purified by distillation from sodium and benzophenone, methylene chloride and toluene were dried by distillation from CaH₂. Flash column chromatography was performed on silica gel (Merck-Kieselgel 60, 230–400 mesh). HRMS were performed by the Centre Régional de Microanalyses (Université Pierre et Marie Curie, Paris VI). Microwave irradiation experiments were performed using a single-mode Initiator TM EXP (0–300 W, 2.45 GHz) from Biotage.

5.2. Reductive amination: compounds 2, 9–13

5.2.1. (S)-2-Cyclohexylamino-3-phenylpropan-1-ol (2)

To a stirred suspension of (S)-2-amino-3-phenylpropan-1-ol (1.01 g, 6.6 mmol) and cyclohexanone (690 μL, 6.6 mmol, 1 equiv) in 1.2-dichloroethane (23 mL) were successively added NaBH(OAc)₃ (2.1 g, 9.9 mmol, 1.5 equiv) and AcOH (0.38 mL, 6.6 mmol, 1 equiv). After stirring at rt for 12 h, the reaction mixture was hydrolyzed by addition of an aqueous 1 M NaOH solution. The aqueous layer was extracted with CH₂Cl₂ and the combined organic phases were washed with an aqueous 1 M NaOH solution, dried over MgSO₄ and filtered. The solvent was removed in vacuo and the residue was purified by flash column chromatography on silica gel (EtOAc: 0.5% Et₂N) to give 2 (1.33 g, 5.7 mmol, 85%). [α]D + 11.57 (c 0.55, CHCl₃); IR (neat) 3272, 3026, 2849, 1600, 1492, 1477, 1350, 1122, 1037, 805, 698 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.32–7.15 (m, 5H), 3.54 (dd, J = 10.4, 1.1 Hz, 1H), 3.23 (dd, J = 10.4, 5.6 Hz, 1H), 3.0 (td, J = 6.8, 5.7, 4.2 Hz, 1H), 2.78–2.67 (m, 2H), 2.45 (tt, J = 10.2, 3.8 Hz, 1H), 2.12 (br s, 2H), 1.85 (m, 1H), 1.75–1.54 (m, 4H), 1.29–0.8 (m, 5H, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 138.7 (s), 129.2 (d, 2C), 128.5 (d, 2C), 126.3 (d, 63.1 (t), 56.8 (d), 53.7 (d), 38.7 (t), 34.3 (t), 33.9 (t), 26.0 (t), 25.0 (t), 24.9 (t); MS-EI m/z (relative intensity): 202 (M⁺-CH₂OH, 32), 142 (100), 132 (13), 120 (33), 105 (8), 91 (36), 83 (12), 60 (35), 55 (16); HRMS calcd for C₁₅H₂₄NO (MH⁺): 234.18524, found: 234.18539.

5.2.2. (S)-2-Benzylamino-3-phenylpropan-1-ol (9)

To a suspension of molecular sieves 4 Å (1.274 g, 5.3 mmol, 80%) in THF, MW, 110 °C, 12 h were successively added (CF₃CO)₂O (1 equiv) and benzaldehyde (670 μL, 6.6 mmol, 1 equiv). After stirring at rt for 12 h, the reaction mixture was hydrolyzed by addition of a saturated aqueous solution of NH₄Cl and concentrated under reduced pressure. The residue was dissolved in EtOH (13 mL) and sodium borohydride was added (294 mg, 7.9 mmol, 1.2 equiv). After stirring at rt for 12 h, the reaction mixture was hydrolyzed by addition of an aqueous 1 M NaOH solution followed by the extraction with CH₂Cl₂, the organic phase was dried over MgSO₄ and filtered. The solvent was removed in vacuo and the residue was purified by flash column chromatography on silica gel (EtOAc: 0.5% Et₂N) to give 9 (1.274 g, 5.3 mmol, 80%).
and concentrated under reduced pressure. The residue was dissolved in EtOH (7 mL) and NaBH₄ was added (150 mg, 4 mmol, 1.2 equiv). After stirring at rt for 12 h, the reaction mixture was hydrolyzed by addition of a saturated aqueous solution of NaH₂PO₄ and concentrated under reduced pressure. Basification of the aqueous residue with an aqueous 1 M NaOH solution was followed by the extraction with CH₂Cl₂ and the combined organic phases were dried over MgSO₄ and filtered. The solvent was removed in vacuo and the residue was purified by flash column chromatography on silica gel (CH₂Cl₂/EtOAc 50/50–50/100) to give 10 (814 mg, 2.8 mmol, 84%).[3] β-J=5.25–5.2 (c 1.0, CHCl₃); IR (neat) 3500–2600, 2334, 1596, 1495, 1460, 1533, 1229, 1116, 1054, 1028, 963, 881, 842, 774, 747, 700 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.83 (m, 1H), 7.75 (d, J=8.0 Hz, 1H), 7.48–7.32 (m, 4H), 7.29–7.13 (m, 5H), 4.21 (d, J=12.8 Hz, 1H), 4.16 (d, J=12.8 Hz, 1H), 3.71 (dd, J=10.8, 4.0 Hz, 1H), 3.38 (dd, J=10.8, 5.3 Hz, 1H), 3.06 (m, 1H), 2.83 (dd, J=13.8, 7.3 Hz, 1H), 2.79 (dd, J=13.6, 6.8 Hz, 1H), 1.98 (br s, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 138.4 (s), 135.5 (s), 133.9 (s), 131.7 (s), 129.2 (d, 2C), 128.8 (d), 128.6 (d), 128.1 (d), 126.5 (d), 126.3 (d), 126.2 (d), 125.7 (d), 125.4 (d), 123.4 (d), 62.8 (t), 60.1 (d), 49.3 (t), 38.2 (t); MS-El/m/z (relative intensity): 273 (M⁺–H₂O, 6), 260 (6), 200 (26), 141 (100), 132 (20), 115 (17), 91 (8); HRMS calcd for C₂₉H₂₈NO (MH⁺): 292.16959; found: 292.16905.

5.2.4. (S)-2-(Heptan-4-ylamino)-3-phenylpropan-1-ol (11)

To a stirred suspension of (S)-2-amino-3-phenylpropan-1-ol (500 mg, 3.3 mmol) and 4-heptanone (460 µL, 3.3 mmol, 1 equiv) in 1,2-dichloroethane (12 mL) were successively added NaBH(OAc)₃ (1.05 g, 5 mmol, 1.5 equiv) and AcOH (0.20 mL, 3.3 mmol, 1 equiv). After stirring at rt for 12 h, the reaction mixture was hydrolyzed by addition of an aqueous 1 M NaOH solution. The aqueous layer was extracted with CH₂Cl₂ and the combined organic phases were washed with an aqueous 1 M NaOH solution, dried over MgSO₄, and filtered. The solvent was removed in vacuo and the residue was purified by flash column chromatography on silica gel (EtOAc–0.5% Et₃N) to give 11 (416 mg, 1.17 mmol, 51%).[3] β-J=5.8–5.8 (c 1.0, CHCl₃); IR (neat) 3500–2600, 2327, 1598, 1510, 1445, 1371, 1262, 1149, 879, 851, 790, 765, 731 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.82 (d, J=13.8 Hz, 1H), 7.79 (d, J=11.7 Hz, 1H), 7.77 (dd, J=10.8, 7.5 Hz, 1H), 7.59–7.39 (m, 4H), 4.31 (d, J=12.8 Hz, 1H), 4.19 (d, J=12.8 Hz, 1H), 3.63 (dd, J=10.5, 4.0 Hz, 1H), 3.29 (dd, J=10.8, 7.0 Hz, 1H), 2.95 (m, 1H), 1.91 (br s, 2H), 1.15 (d, J=6.3 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 135.9 (s), 134.0 (s), 131.8 (s), 128.8 (d), 128.0 (d), 126.3 (d), 126.2 (d), 125.7 (d), 125.4 (d), 123.4 (d), 62.9 (t), 60.5 (d), 57.5 (d), 39.1 (t), 37.3 (t), 36.4 (t), 18.9 (t), 18.3 (t), 14.4 (q), 14.3 (q); MS-El/m/z (relative intensity): 216.13829; found: 216.13817.

5.3. Rearrangement: compounds 3, 4, 6, 14–18

5.3.1. Typical procedure

To a solution of β-aminococohol of type E in THF (0.5 M) was added dropwise trifluoroacetic anhydride (1 equiv) and then Et₃N (1 equiv). The reaction mixture was then heated under microwave irradiation in a sealed tube. After addition of an aqueous 2.5 M NaOH solution (2 mL), the mixture was stirred at rt for 2 h, extracted with EtOAc, dried over MgSO₄, filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel afforded β-aminocob alcohol of type D.

5.3.2. (R)-1-Benzylamino-2-propan-1-ol (3)[15]

Following the typical procedure (120 °C, 12 h, MW), the transformation of 1 (100 mg, 0.6 mmol) afforded an oil that was purified by flash column chromatography on silica gel (EtOAc/MeOH/90/10–0.5% Et₃N) to give 3 (88 mg, 0.53 mmol, 88%).[3] β-J=28–28 (c 0.50, CHCl₃); IR (neat) 2825, 1673, 1495, 1453, 1374, 1201, 1136, 1028, 918, 841, 736, 697 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.32–7.15 (m, 5H), 3.74 (d, J=13.3 Hz, 1H), 3.73 (m, 1H), 3.69 (d, J=13.3 Hz, 1H), 3.0 (m, 1H), 2.60 (dd, J=10.7, 4.0 Hz, 1H), 2.35 (dd, J=10.7, 7.0 Hz, 1H), 1.07 (d, J=6.4 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 139.7 (s), 128.5 (d, 2C), 128.3 (d, 2C), 127.2 (d), 65.5 (t), 54.4 (d), 49.0 (t), 173 (q); HRMS calcd for C₁₅H₁₄NO (MH⁺): 250.11594; found: 250.11641.

5.3.3. (R)-1-Cyclohexylamino-3-phenylpropan-1-ol (4)

Rearrangement with a catalytic amount of H₂SO₄. To a solution of (S)-2-cyclohexylamino-3-phenylpropan-1-ol (4) (200 mg, 0.86 mmol, 1.0 equiv) in THF (1 mL) was added dropwise sulfuric acid (3 µL, 0.04 mmol, 0.05 equiv). The reaction mixture was then heated at 180 °C for 24 h under microwave irradiation in a sealed tube. After addition of the saturated aqueous NaHCO₃ solution, the mixture was extracted with EtOAc, dried over MgSO₄, filtered, and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (EtOAc–0.5% Et₃N) afforded 4 (84 mg, 0.36 mmol, 42%).
Rearrangement with a catalytic amount of TFA. To a solution of 3-phenylpropan-1-ol in THF (1 mL) was added dropwise trifluoroacetic acid (4 μL, 0.05 mmol, 0.06 equiv). The reaction mixture was then heated at 180 °C for 24 h under microwave irradiation in a sealed tube. After addition of an aqueous 2.5 M NaOH solution (1 mL), the mixture was stirred at rt for 2 h, extracted with EtOAc, dried over MgSO4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (CH2Cl2/EtOAc=0.5% Et3N) afforded 4 (114 mg, 0.49 mmol, 57%).

Rearrangement with a catalytic amount of TFAA. To a solution of 3-phenylpropan-1-ol in THF (1 mL) was added dropwise trifluoroacetic anhydride (7 μL, 0.05 mmol, 0.06 equiv). The reaction mixture was then heated at 180 °C for 20 h under microwave irradiation in a sealed tube. After addition of an aqueous 2.5 M NaOH solution (1 mL), the mixture was stirred at room temperature for 2 h, extracted with EtOAc, dried over MgSO4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (CH2Cl2/EtOAc=0.5% Et3N) afforded 4 (107 mg, 0.46 mmol, 54%).

Rearrangement with a stoichiometric amount of TFAA and Et3N. Following the typical procedure (110 °C, 6 h, MW), the transformation of 2 (91 mg, 0.39 mmol) afforded an oil that was purified by flash column chromatography on silica gel (EtOAc=0.5% Et3N) to give 4 (77 mg, 0.33 mmol, 85%).

Following the typical procedure (110 °C, 6 h, MW), the transformation of 5 (54 mg, 0.24 mmol) afforded an oil that was purified by flash column chromatography on silica gel (EtOAc=0.5% Et3N) to give 6 (39 mg, 0.17 mmol, 72%).

Following the typical procedure (120 °C, 12 h, MW), the transformation of 9 (104 mg, 0.43 mmol) afforded an oil that was purified by flash column chromatography on silica gel (EtOAc=0.5% Et3N) to give 14 (72 mg, 0.30 mmol, 70%).

Following the typical procedure (120 °C, 12 h, MW), the transformation of 10 (100 mg, 0.52 mmol) afforded an oil that was purified by flash column chromatography on silica gel (CH2Cl2/EtOAc=50/50=0.5% Et3N) to give 15 (79 mg, 0.27 mmol, 80%).

Following the typical procedure (120 °C, 12 h, MW), the transformation of 10 (100 mg, 0.52 mmol) afforded an oil that was purified by flash column chromatography on silica gel (CH2Cl2/EtOAc=50/50=0.5% Et3N) to give 15 (79 mg, 0.27 mmol, 80%).
chromatography on silica gel afforded \(N,N\)-dibenzyl or \(N,N\)-benzyl-alkyl \(\beta\)-amino alcohol.

**Method B.** A mixture of \(N\)-naphthyl \(\beta\)-amino alcohol, ammonium formate (10 equiv), and 10% \(\text{Pd/C}\) (25 mg) in \(\text{MeOH}\) (5 mL) was stirred at reflux for 4 h. The reaction media is filtered on Celite and concentrated under reduced pressure. The residue was mixed with benzyl bromide (2.2 equiv), \(K_2\text{CO}_3\) (3 equiv), and \(\text{MeOH}\) (5 mL) and was stirred at reflux for 4 h. The reaction media was concentrated under reduced pressure and the residue was dissolved in water (10 mL) and ethyl acetate (10 mL). Aqueous phase was extracted three times with ethyl acetate and the combined organic extracts were dried over MgSO\(_4\), filtered, and concentrated in vacuo. Purification of the crude residue by flash chromatography on silica gel afforded \(N,N\)-dibenzyl-\(\beta\)-amino alcohol.

5.4.1. \((S)-2,N,N\)-Dibenzylamino-1-phenylethanol (19)\(^{11}\)

Method A was used to prepare 19 from 6. The transformation of 6 (29 mg, 0.13 mmol) led to an oil that was purified by flash column chromatography on silica gel (petroleum ether/\(\text{EtOAc}\) 95/5) to give 19 (35 mg, 0.11 mmol, 88%); \(\delta\)\(^{13}C\) = 67.5 (t), 54.6 (t), 41.3 (t), 33.7 (t), 31.4 (t), 20.7 (t), 20.3 (t), 14.1 (q); MS-EI \(m/z\) (relative intensity): 354.27914; found: 354.27917.

Method B was used to prepare 19 from 16. The transformation of 16 (55 mg, 0.22 mmol) led to an oil that was purified by flash column chromatography on silica gel (petroleum ether/\(\text{EtOAc}\) 97.5/2.5) to give 19 (67 mg, 0.25 mmol, 90%); \(\delta\)\(^{13}C\) = 67.5 (t), 54.6 (t), 41.3 (t), 33.7 (t), 31.4 (t), 20.7 (t), 20.3 (t), 14.1 (q); MS-EI \(m/z\) (relative intensity): 353.27914; found: 353.27920.

5.4.2. \((R)-1-N,N\)-Dibenzylaminopropan-2-ol (20)\(^{11}\)

Method A was used to prepare 20 from 3. The transformation of 3 (29 mg, 0.13 mmol) led to an oil that was purified by flash column chromatography on silica gel (petroleum ether/\(\text{EtOAc}\) 95/5) to give 20 (35 mg, 0.11 mmol, 85%).

Method B was used to prepare 20 from 18. The transformation of 18 (49 mg, 0.23 mmol) led to an oil that was purified by flash column chromatography on silica gel (petroleum ether/\(\text{EtOAc}\) 90/10) to give 20 (30 mg, 0.12 mmol, 51%). \(\varepsilon\) = 93% determined by supercritical fluid chromatography on Daicel chiralpack OD-H column (MeOH 20%, flow rate 8 mL/min, \(t\) \(\beta\) (major) = 1.4 min, \(t\) \(\alpha\) (minor) = 1.9 min).

5.4.3. \((R)-1-N,N\)-Dibenzylamino-3-phenylpropan-2-ol (21)\(^{11}\)

Method A was used to prepare 21 from 14. The transformation of 14 (44 mg, 0.27 mmol) led to an oil that was purified by flash column chromatography on silica gel (petroleum ether/\(\text{EtOAc}\) 90/10) to give 21 (56 mg, 0.22 mmol, 82%).

Method B was used to prepare 21 from 21. The transformation of 21 (48 mg, 0.22 mmol) led to an oil that was purified by flash column chromatography on silica gel (petroleum ether/\(\text{EtOAc}\) 90/10) to give 21 (29 mg, 0.11 mmol, 52%). \(\varepsilon\) = 98% from 14) and 96% (from 15) determined by supercritical fluid chromatography on Daicel chiralpack OD-H column (MeOH 10%, flow rate 8 mL/min, \(t\) \(\beta\) (major) = 2.1 min, \(t\) \(\alpha\) (minor) = 2.6 min).

5.4.4. \((R)-1-(Benzyloxyethylamino)-3-phenylpropan-2-ol (22)\(^{11}\)

Method A was used to prepare 22 from 4. The transformation of 4 (42 mg, 0.18 mmol) led to an oil that was purified by flash column chromatography on silica gel (cyclohexane/\(\text{EtOAc}\) 95/5) to give 22 (55 mg, 0.17 mmol, 94%); \(\delta\)\(^{13}C\) = 67.5 t), 54.6 (t), 41.3 (t), 33.7 (t), 31.4 (t), 20.7 (t), 20.3 (t), 14.1 (q); MS-EI \(m/z\) (relative intensity): 311.27914; found: 311.27920.

To a solution of D-serine methyl ester hydrochloride (2 g, 12.9 mmol) and \(\text{K}_2\text{CO}_3\) (3.86 g, 36.8 mmol, 3 equiv) in \(\text{H}_2\text{O}\) (350 mL) was added at 0 °C a solution of benzyl chloroformate (2.02 mL, 21.5 mmol, 2.2 equiv) and \(\text{TsOH}\) (0.3 equiv) in \(\text{MeOH}\) (350 mL). The organic layer was dried over MgSO\(_4\) and evaporated. The crude oil was dissolved in 2,2-dimethoxypropane (35 mL, 285 mmol, 22 equiv) and \(\text{TsOH}\) \(\text{H}_2\text{O}\) (350 mg, 1.8 mmol, 0.14 equiv) was added. The reaction mixture was refluxed for 4 h and then concentrated under reduced pressure. The residue was dissolved in \(\text{EtOAc}\) (100 mL) and washed with aqueous NaHCO\(_3\) (2 x 50 mL). The organic layer was dried over MgSO\(_4\) and evaporated in vacuo and the residue purified by flash chromatography (silica gel, petroleum ether/\(\text{EtOAc}\) 90/10) to afford (S)-3-benzyl-4-methyl-
5.5.4. (S)-Benzy1-2,2-dimethyl-4-[[naphthalen-1-yloxy]methyl]oxazolidine-3-carboxylate (28)

To a solution of 25 (418 mg, 1.6 mmol) x-naphthol (341 mg, 2.4 mmol, 1.5 equiv) and triphenylphosphine (621 mg, 2.4 mmol, 1.5 equiv) in toluene (4 mL) was added DEAD (40 wt% solution in toluene; 1 mL, 2.4 mmol, 1.5 equiv). The reaction mixture was stirred for 18 h at 80 °C in a sealed tube. The solvent was evaporated and the residue was dissolved in EtOAc (20 mL), washed with an aqueous 2.5 M NaOH solution (10 mL), dried with MgSO4 filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc 92/8) to give 28 (413 mg, 1.06 mmol, 67%). [M+H]+ (447.0, CI); IR (neat) 2877, 1700, 1580, 1402, 1348, 1237, 1205, 1107, 837, 676, 597 cm⁻¹; 1H NMR (400 MHz, CDCl3): δ 8.26 (d, J = 7.8 Hz, 1H), 7.78 (d, J = 8.3 Hz, 1H), 7.50–7.73 (3H, 7H), 7.16 (dd, J = 7.9, 7.9 Hz, 1H), 6.70 (d, J = 7.5 Hz, 1H), 5.19 (m, 2H), 4.41 (m, 1H), 4.28 (m, 2H), 4.11 (m, 2H), 1.71 (s, 3H), 1.59 (s, 3H); (minor rotamer) δ 8.26 (d, J = 8.0 Hz, 1H), 7.78 (d, J = 8.3 Hz, 1H), 7.50–7.73 (3H, 7H), 6.96 (d, J = 7.5 Hz, 1H), 5.19 (m, 2H), 4.52 (m, 1H), 4.28 (m, 2H), 4.11 (m, 2H), 1.63 (s, 3H), 1.52 (s, 3H); 13C NMR (100 MHz, CDCl3): (major rotamer) δ 153.8 (s), 152.3 (s), 136.2 (s), 134.5 (s), 128.7 (d, 2C), 128.3 (d, 3C), 127.5 (d, 125.6 (d), 125.5 (d), 125.3 (d), 121.8 (d), 120.7 (d), 104.9 (d), 94.6 (s), 67.1 (t), 66.7 (t), 65.8 (t), 55.6 (d), 26.7 (q), 23.1 (q); (minor rotamer) δ 154.1 (s), 153.2 (s), 134.5 (s), 128.7 (d, 2C), 128.1 (d, 3C), 127.5 (d), 126.4 (d), 120.5 (d), 120.2 (d), 120.6 (d), 105.0 (d), 94.1 (s), 67.5 (t), 66.2 (t), 65.6 (d), 27.6 (q), 24.5 (q); MS-El m/z (relative intensity): 391 (M⁺), 248 (13), 190 (12), 127 (6), 115 (6), 91 (100), 65 (3); HRMS calcld for C24H24NO4Na (MNa⁺): 414.16785; found: 414.16829.

5.5.5. (R)-2-(Isopropylamino)-3-(naphthalen-1-yloxy)propan-1-ol (29)

A solution of 28 (220 mg, 0.56 mmol) in EtOH (55 mL) was hydrodengated in a flow manner using the H-Cube (Thales Nanotechnology Inc.) operating at 10–15 bars of in situ H2 pressure at rt with a flow rate of 1 mL/min. The catalyst bed (Cat-Carb™ Pd/C 10% w/w) was available from Thales. The solvent was evaporated and the residue was purified by flash chromatography on silica gel (EtOAc/MeOH 99/1) to give 29 (109 mg, 0.42 mmol, 75%); [M+H]+ +251 (c 1.5, CHCl3); IR (neat) 3200–2500, 2327, 1578, 1506, 1455, 1403, 1272, 1241, 1099, 1046, 955, 870, 765 cm⁻¹; 1H NMR (400 MHz, CDCl3): δ 8.23 (m, 1H), 7.84 (m, 1H), 7.55–7.46 (m, 3H), 7.40 (dd, J = 7.9, 7.9 Hz, 1H), 6.85 (dd, J = 7.5, 0.8 Hz, 1H), 4.22 (dd, J = 5.5, 0.8 Hz, 1H), 4.14 (dd, J = 9.3, 5.5 Hz, 1H), 3.83 (dd, J = 10.8, 4.5 Hz, 1H), 3.68 (dd, J = 10.8, 5.8 Hz, 1H), 3.22 (dd, J = 5.5, 5.8 Hz, 1H), 3.08 (qq, J = 6.2, 6.2 Hz, 1H), 2.43 (br s, 2H), 1.85 (br s, 2H), 1.18 (d, J = 6.5 Hz, 3H), 1.16 (d, J = 6.5 Hz, 3H); 13C NMR (100 MHz, CDCl3): δ 154.3 (s), 134.5 (s), 127.6 (d), 126.5 (d), 125.9 (s), 125.4 (s), 121.6 (d), 120.7 (d), 104.7 (d), 68.0 (t), 61.8 (t), 55.5 (d), 46.3 (d), 23.7 (q), 23.5 (q); MS-El m/z (relative intensity): 244 (M⁺), 199, 165 (83), 152 (19), 115 (17), 56 (10); HRMS calcld for C25H25NO3Na (MNa⁺): 383.1717; found: 383.1720.
then Et₃N (17 μL, 0.12 mmol, 1 equiv). The reaction mixture was then heated at 110 °C for 12 h under microwave irradiation in a sealed tube. After addition of an aqueous 2.5 M NaOH solution (2 mL), the mixture was stirred at rt for 2 h, extracted with EtOAc, dried over MgSO₄, filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (EtOAc/MeOH 90/10 + 0.5% Et₃N) afforded (S)-toliprolol (19 mg, 0.08 mmol, 69%). ¹H NMR (400 MHz, CDCl₃): δ 7.16 (dd, J = 7.8, 7.8 Hz, 1H), 6.79–6.76 (m, 1H), 6.75–6.70 (m, 2H), 4.05–3.92 (m, 3H), 2.88 (dd, J = 12.0, 3.8 Hz, 1H), 2.82 (t, J = 6.3 Hz, 1H), 2.72 (dd, J = 12.0, 7.0 Hz, 1H), 2.52 (br s, 2H), 2.32 (s, 3H), 1.09 (d, J = 6.3 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃): δ 158.7 (s), 139.6 (s), 129.2 (d), 121.9 (d), 115.4 (d), 111.4 (d), 70.4 (t), 68.4 (d), 49.4 (t), 49.0 (d), 23.0 (q), 22.9 (q), 21.5 (q); MS-EL m/z (relative intensity): 223 (M⁺, 1), 208 (3), 179 (8), 91 (13), 72 (100), 56 (11); HRMS calcd for C₁₁H₂₂NO (MH⁺): 224.16451; found: 224.16481.

5.5.7. (S)-Propanolol

To a solution of 29 (54 mg, 0.21 mmol) in THF (1 mL) was added dropwise trifluoroacetic anhydride (30 μL, 0.21 mmol, 1 equiv) and then Et₃N (30 μL, 0.21 mmol, 1 equiv). The reaction mixture was then heated at 110 °C for 12 h under microwave irradiation in a sealed tube. After addition of an aqueous 2.5 M NaOH solution (2 mL), the mixture was stirred at rt for 2 h, extracted with EtOAc, dried over MgSO₄, filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (EtOAc/MeOH 90/10 + 0.5% Et₃N) afforded (S)-propanolol (32 mg, 0.12 mmol, 60%). [α]D²⁰ = -7.6 (c 0.9, EtOH) [lit 5 [α]D²⁰ = -9.9 (c 0.83, EtOH)]; mp 52–54 °C; ee = 92% determined by supercritical fluid chromatography on Daicel chiralpak OD-H column (MeOH/Et₃N 99.5/0.5 15%, flow rate 3 mL/min, tθ (major) = 7.4 min, tθ (minor) = 4.7 min); IR (neat) 3200–2500, 1596, 1582, 1459, 1401, 1341, 1268, 1241, 1101, 1067, 1020, 941, 787, 762 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 8.17 (m, 1H), 7.72 (m, 1H), 7.44–7.35 (m, 3H), 7.29 (dd, J = 7.9, 7.9 Hz, 1H), 6.75 (d, J = 7.5 Hz, 1H), 4.13–4.03 (m, 3H), 2.92 (dd, J = 12.0, 3.3 Hz, 1H), 2.83–2.73 (m, 2H), 2.35 (br s, 2H), 1.03 (d, J = 6.3 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃): δ 154.3 (s), 134.5 (s), 127.6 (d), 126.5 (d), 125.9 (s), 125.6 (s), 125.3 (d), 121.9 (d), 120.7 (d), 104.9 (d), 70.7 (t), 68.5 (d), 49.5 (t), 49.0 (d), 23.2 (q), 23.1 (q); MS-EL m/z (relative intensity): 259 (M⁺, 5), 215 (5), 144 (17), 127 (9), 115 (28), 72 (100), 56 (10); HRMS calcd for C₁₅H₂₄NO (MH⁺): 260.16451; found: 260.16479.

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References and notes